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Biomarkers Associated With Response to the CAR-T Cell Therapy LB2102 in Subjects with SCLC or LCNEC

Authors: Jacob Sands MD[1], Alberto Chiappori MD[2], Ben Creelan MD[2]; Reinhold Munker, MD[3]; Paul Schwarzenberger, MD[4]; Sahista Vahora, PharmD[4]; Christian Davis, MS[4]; Chuan Wang, PhD[4]; Jinghui Zhang, PhD[4]; Lijun Xin, PhD[4]; Jieqing Zhu[4], Sifan Xu[4], Ying He PhD[4], Dong Geng PhD[4], Adam J. Schoenfeld, MD[5]; Zhonglin Hao, MD PhD[3]

[1]Dana Farber Cancer Institute, Boston MA; [2]Moffitt Cancer Center, Tampa FL; [3]Markey Comprehensive Cancer Center, University of Kentucky; [4]Legend Biotech USA Inc, Somerset NJ; [5]Memorial Sloan Kettering Cancer Center, New York City NY

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Introduction

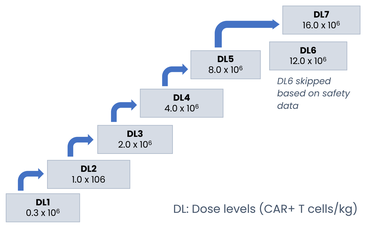
- Delta-like ligand 3 (DLL3) is an inhibitory Notch ligand highly expressed in neuroendocrine tumors including small cell lung carcinoma (SCLC) and large cell neuroendocrine lung carcinoma (LCNEC), with minimal expression in normal tissues
- LB2102 is an autologous chimeric antigen receptor T-cell (CAR-T) immunotherapy comprising a CAR-specific to DLL3 and dominant-negative transforming growth factor-β receptor type II (dnTGFBR2)
- The dnTGFBR2 removes the inhibitory effects of TGF-β on the CAR-T cells, increase the survival and activity of CAR-T cells in the hostile tumor microenvironment
- This analysis explores biomarkers associated with clinical response

Methods

Study Design:

- LB2102 is first-in human phase I, open label, multi-center study to evaluate the safety and efficacy for treatment of SCLC or LCNEC (**Figure 1**)
- Key eligibility criteria include unresectable SCLC or LCNEC, ≥1 prior line of systemic treatment and have progressed after or have had an insufficient response
- Subjects received LB2102 at 6 dose levels (DLs 1–7, DL6 skipped) (0.3–16.0×10^6 CAR-T cells/kg).

Figure 1. Dose Escalation Design, Study Flow, and Dose Levels



Endpoints and assessments:

- Primary Objective: To characterize the safety and tolerability of LB2102 and determine the recommended dose for expansion
- Secondary Objective: To evaluate the preliminary efficacy, pharmacokinetics and immunogenicity
- Blood samples, as well as drug product samples were analyzed by qPCR, flow cytometry, and MSD immunoassays
- Biopsies were analyzed by immunohistochemistry. DLL3 expression was quantified based on estimation of the percentage of positive tumor cells
- Circulating Tumor Cells (CTC) were evaluated by CellSearch CTC assay. Total CTCs were enumerated as CK+CD45-DAPI+ cells. DLL3+ CTCs include: DLL3+CK+CD45$^-$DAPI+, DLL3dim CK+CD45$^-$DAPI+, and DLL3+CK$^-$CD45-DAPI+ cells
- Correlative analyses were performed with the best confirmed response

Statistical methodology:

- Two-group comparison: nonparametric Wilcoxon test

Baseline Demographics and Characteristics

- The study population comprised 20 subjects with relapsed and/or refractory (R/R) SCLC or LCNEC
- 17/20 (85%) subjects had SCLC, 14/20 (70%) with extensive-stage disease at diagnosis
- Subjects had history of previously treated brain metastases
- 95% of subjects received bridging therapy while waiting for CAR-T cell manufacturing, including brain radiation in 40% of subjects

Safety

Safety was Manageable, With no DLTs or LB2102-related Deaths

TEAEs Grade ≥ 3

- Related to LB2102 in 10 subjects(50%)
- 1 death from pneumonia (not related to LB2102)
- Most LB2102-related are hematologic and associated with lymphodepletion

CRS occurred in 6 subjects (30%)

- Grade 1 n=4, Grade 2 n=2
- 3 subjects treated with tocilizumab, 2 treated with steroids
- Median onset 2.5 days (1, 16 days)
- Median duration 2.5 days (1, 7 days)

ICANS occurred in 3 subjects (15%)

- Grade 1 in 2 subjects and Grade 3 in 1 subject
- Median onset 4 days (4, 5 days)
- Median duration 5 days (2, 7 days)

Efficacy

Clinical Activity Observed at DL3 and Above

At DL3 and above (n=14)

SCLC: objective response rate (ORR) 33.3% (4/12); disease control rate 83.3% (10/12)
LCNEC: ORR 0% (0/2); disease control rate 50.0% (1/2)

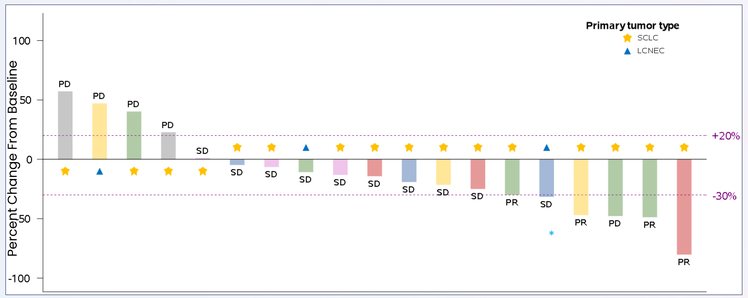
Median Duration of Response was 6.5 mo (95% CI, 6.1-NR)

Ongoing response in 2 subjects (median follow up 17.6 mo; range 1.1, 19.5 mo)

At ≥ DL3 (median follow up 12.5 mo; range 1.1, 18.1 mo)

Median Duration of Disease Control was 6.1 mo (95% CI, 1.3-6.8 mo)
Disease Control Rate was 60.6% at 6 mo and 15.2% at 9 mo

Figure 2. Best Percent Change from Baseline in Target Tumor Lesion Size



PR: Partial response | SD: Stable disease | PD: Progressive disease | LCNEC: Large cell neuroendocrine lung cancer | SCLC: Small cell lung cancer

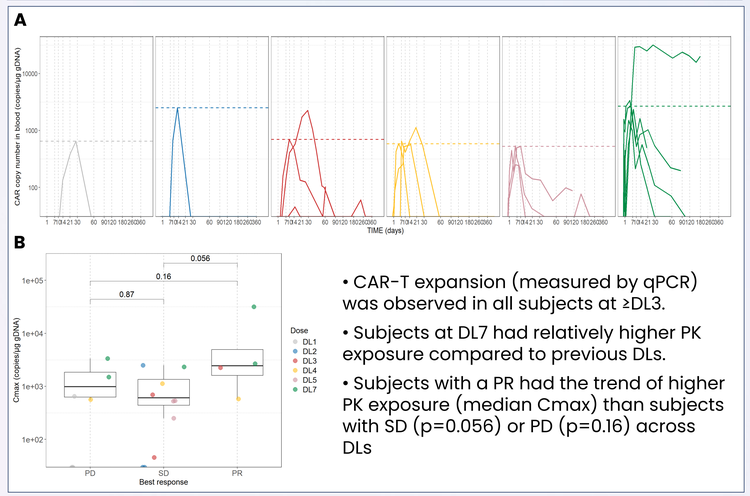
Notes: The best percent change from baseline was not evaluable in 1 subject due to non-measurable disease at baseline per RECIST criteria, and thus, it is not presented in the figure.

Although the subject's best overall response was SD, a 31.6% reduction in target lesion size was observed at the PD assessment; PD was declared due to the appearance of a new lesion

Data Cutoff: 31JUL2026

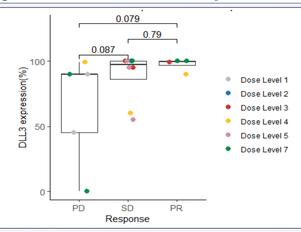
Pharmacokinetics and Biomarkers

Figure 3. CAR Transgene Levels Associate with Dose Level (A) and Response (B)



- CAR-T expansion (measured by qPCR) was observed in all subjects at ≥DL3.
- Subjects at DL7 had relatively higher PK exposure compared to previous DLs.
- Subjects with a PR had the trend of higher PK exposure (median Cmax) than subjects with SD (p=0.056) or PD (p=0.16) across DLs

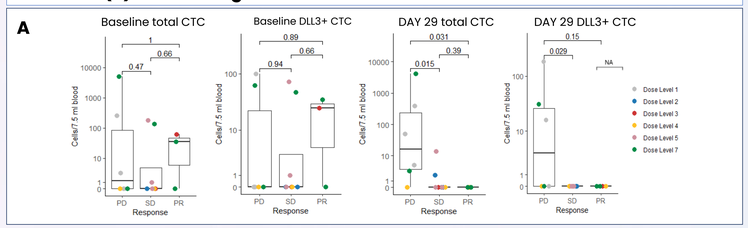
Figure 4. DLL3 Baseline Expression Does not Correlate With Response



Overall, 76% (13/17) of evaluable subjects had baseline DLL3 expression ≥ 90%

There is no correlation of baseline DLL3 expression with clinical response

Figure 5. (A) Total CTC and DLL3+ CTC Count Associate With Response (B) CAR Transgene C_{max} Associates with Detection of CTCs

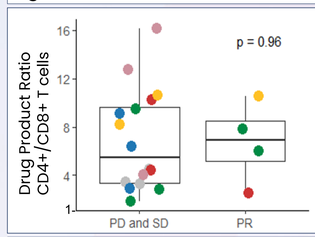


- Total circulating tumor cells (CTCs) and DLL3+ CTCs were detected in 8/18 (44%) and 7/18 evaluable subjects (39%) at baseline, respectively
- At Day 29 after LB2102 infusion, total CTCs and DLL3+ CTCs were detectable in 5/6 (83%) and 3/6 (50%) subjects with PD; 2/9 (22%) and 0/9 subjects with SD; and 0/4 and 0/4 subjects with PR, respectively

Subjects with detectable CTCs (DLL3+ or not) had a trend of higher CAR-T cell expansion (higher median C_{max}) than subjects with undetectable CTCs However, due to limited sample size, there is no statistical significance.

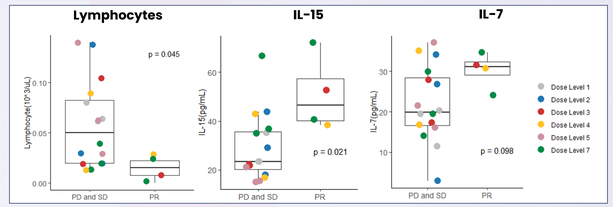
Biomarkers

Figure 6. Ratio of CAR-T CD4+:CD8+ Cells and Clinical Response



The ratio of CAR CD4+:CD8+ T cells in LB2102 drug product does not associate with clinical response

Figure 7. Pre-infusion Lymphocytes and IL-15 Associate With Response



- Lymphodepletion reduces the number of endogenous lymphocytes that consume homeostatic cytokines such as IL-7 and IL-15. This results in higher levels of IL-7 and IL-15, which promote CAR-T cell expansion
- Subjects with a PR had a lower mean baseline (Day 1, pre-infusion) lymphocyte count (p=0.04) and higher mean IL-15 level (p=0.02) vs non-responders

Conclusions

- The CAR-T therapy LB2102 showed a favorable safety profile in a Phase 1, first in human trial of 20 subjects with refractory or relapsed SCLC or LCNEC, across 6 dose levels, with no DLTs
  - CRS and ICANs are manageable
- LB2102 showed encouraging antitumor activity at doses ≥ 2 million CAR-T cells (≥DL3) per kg body weight, in the subjects. Responses seem durable supporting further investigation
- CAR-T expansion (measured by qPCR) was observed in all subjects at ≥DL3. Although there was no clear dose-dependent expansion, subjects at DL7 had relatively higher PK exposure compared to previous DLs
- Subjects with a PR had the trend of higher PK exposure than subjects with SD or PD across DLs
- Immunohistochemical analyses showed no correlation between baseline DLL3 expression and clinical response
- Although total and DLL3+ CTCs at baseline did not correlate with clinical response, total and DLL3+ CTCs at Day 29 in most patients with SD and PR were reduced to non-detectable.
- The ratio of CAR-T CD4+:CD8+ cells in the LB2102 drug product was not associated with clinical response
- Low Day 1 pre-infusion lymphocyte count and high IL-15 and IL-7 levels associate with better clinical response

Acknowledgements

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